REMARKS

Interview Request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative, as noted below.

Supplemental Information Disclosure Statement

Applicants herein submit a supplemental IDS to the Office. It is respectfully requested that the information cited therein be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the "references cited" on any patent to issue therefrom.

Status of the Claims

Claims 1, 4, 5, 9, 11-15, 21, 23-28 are pending. Claims 2, 3, 6-8, 10, 16-20, and 22 have been cancelled, without prejudice or disclaimer. Claims 1, 12, 13, 14, and 15 have been amended. New claims 29-39 have been added.

Amendments to the Specification

The title has been amended to more closely reflect the pending claims as currently amended.

Amendments to Claims

Claim 1 has been amended to remove the phrase "or female sexual arousal disorder". This amendment is made without prejudice or disclaimer and has been made solely to expedite prosecution. Claim 1 has also been amended to add the word "male". Support for this amendment can be found in originally filed claim 1. Claim 12 has been amended to specify one exemplary mode of administration of bFGF. Support for this amendment can be found in originally filed claim 5. Claim 13 has been amended to be dependent from claim 1 and to add the phrase "wherein the dysfunction is induced by hypercholesterolemia or induced by a cavernous nerve injury." Support

for this amendment can be found, for example, in Example 5 and at paragraphs 185 and 188 of the specification. Claim 14 has been amended to be dependent from claim 1 and to include the phrase "wherein the male erectile dysfunction is preventable or treatable by increasing neovascularization and the administration of bFGF causes neovascularization thereby preventing or treating the male erectile dysfunction." Support for this amendment can be found, for example, at paragraphs 17 and 134 of the specification. Claim 15 has been amended to be dependent from claim 14 and to specify one exemplary mode of administration of bFGF. Support for this amendment can be found in originally filed claim 5. Claims 29-38 have been added. Support for claim 29 can be found, for example, in originally filed claims 1 and 5 and at paragraphs 17 and 134 of the specification. Support for claims 30-36 can be found, for example, in originally filed claims 1 and 21 and at paragraphs 28 and 83 of the specification. Support for claims 37 and 38 can be found, for example, in originally filed claims 17 and 18 and at paragraphs 31 and 32 of the specification. Support for claim 39 can be found, for example, at paragraphs 80 and 86 of the specification.

No new matter has been added by way of these amendments.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 4, 5, 9, 11-15, and 21-28, are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirements.

Claim 1 prior to the amendment was directed to a method for treating or preventing *either* male erectile dysfunction or female sexual arousal disorder by administering bFGF to a mammal. Claim 1 has been amended to remove the phrase "or female sexual arousal disorder", and to the extent that the rejection pertains to this aspect, it is overcome. Applicants will herein address the Examiner's concerns regarding enablement as they relate to preventing or treating male erectile disorder.

The Examiner states on page three of the Office Action that "the prior art appears to be silent on whether bFGF is effective in preventing or treating male erectile disorder ...." On page four of the Office Action, the Examiner alleges that the "specification does not teach whether bFGF prevent[s] or treat[s] male erectile dysfunction as a result of cavernous nerve damage. The specification also fails to teach whether bFGF can prevent or treat erectile dysfunction caused by

other factors such as arterial insufficiency or venous leakage." The Examiner also asserts that the "specification does not demonstrate that any route of administration would result in the treatment of erectile dysfunction." In addition, the Examiner states that "...whether administering a single factor bFGF by any route would be effective in treating or preventing all types of erectile dysfunction ... is unpredictable." Lastly, the Examiner alleges that "whether administering bFGF to an individual can prevent or treat the claimed disorder is unpredictable because the specification fails to show or provid[e] any working example that administering bFGF to an animal model would prevent or treat the claimed [] disorder."

It appears from the Examiner's comments that the Examiner has concerns regarding whether or not bFGF would work as described in the specification and the pending claims. These concerns appear to be more commensurate with a 35 U.S.C. §§ 101 and 112, first paragraph, enablement rejection.

It should be noted that the Examiner has the initial burden of challenging an asserted utility. Only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)).

Lack of a working example.

The Examiner asserts that the specification fails to show or provide any working example showing that administering bFGF to an animal model would prevent or treat erectile dysfunction, and that one of skill in the art would have to engage in under experimentation to practice the method commensurate in scope with the claims.

First, a working example is not needed for enablement. See *In re Marzocchi*, 439 F2d 220, 169 USPQ 367 (CCPA 1971). MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

Second, the lack of a working example does not establish that the claims are not enabled: an invention can be properly described and claimed without an actual reduction to practice. (MPEP 2164.02: "An applicant need not have actually reduced the invention to practice prior to filing," citing Gould v. Quigg, 3 USPQ2d 1302 (Fed. Cir. 1987). See also MPEP 2164.02: "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).)

The Examiner has not made a *prima facie* case as to why the specification is not enabled.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510 ,1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367 , 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

In addition, according to In re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also In re Brana, 51 F.3d

1560, 1566, 34 USPQ2d 1436 ,1441 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)) (discussed in MPEP Section 2164.07 regarding the relationship of the enablement requirement to the utility requirement of 35 U.S.C. 101).

In *In re Brana*, the Examiner's rejection was based on a challenge of utility of the claimed compounds and the amount of experimentation necessary to use the compounds. The Federal Circuit concluded that "we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness" and that "[e]ven if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility."

The facts of *In re Brana*, are similar to the current application, in that the nature of Applicants' invention alone does *not* cause one of skill in the art to reasonably doubt the asserted usefulness, the PTO has not provided a *prima facie* case regarding lack of utility or enablement, and Applicants *have* proffered sufficient evidence to convince one of skill in the art of the asserted utility.

The specification is enabling.

As stated in the specification at paragraph 177, "[t]he erectile function of the penis is that of a *vascular* organ. Like those of other vascular organs, the development and growth of the penile vasculature are expected to be governed by angiogenic growth factors such as VEGF" (emphasis added). In addition, at paragraph 11, it is described how "the penis is a predominantly *vascular* organ, and *vascular or penile arterial insufficiency* is the most common etiology of erectile dysfunction (ED)" (emphasis added).

Paragraph 4, discloses how "VEGF is a family of proteins that were discovered on the basis of their ability to stimulate VEC growth (*angiogenesis*)" (emphasis added). Angiogenesis is then described at paragraph 6 as "a complex process that includes activation, migration and proliferation of endothelial cells and formation of new blood vessels", and "VEGF has been shown to be intimately involved in the entire sequence of events leading to growth of new blood vessels."

The role of bFGF in angiogenesis is then described in paragraph 9 of the specification.

> "a member of the fibroblast growth factor family. bFGF stimulates the proliferation of all cells of mesodermal origin including smooth muscle cells, neuroblasts, and endothelial cells. bFGF stimulates neuron differentiation, survival, and regeneration. *In vitro* functions suggest that **bFGF modulates angiogenesis**, wound healing and tissue repair, and neuronal function *in vivo*. bFGF, a heparin-binding growth factor, is capable of **inducing functionally significant angiogenesis** in models of myocardial and limb ischemia" (emphasis added).

Therefore, the important role of both bFGF and VEGF in angiogenesis and maintaining the vascular structure of the penis is described in the specification. In addition, the specification describes how the development and growth of the penile vasculature is governed by angiogenic growth factors such as bFGF and VEGF. Lastly, the specification describes how vascular or penile arterial insufficiency is the most common etiology of ED. Therefore, one of skill in the art would, based on the reading of the specification, understand that bFGF, like VEGF, would be useful in the prevention and treatment of ED.

In addition to the specification, the current scientific literature describes the effectiveness of bFGF in preventing and treating male erectile dysfunction, as discussed below.

Therefore, the specification *does* teach how to make and use the claimed invention. Specifically, the specification provides a rational as to why bFGF would work in preventing and treating ED. Also, the scope of any enablement provided by the specification to one of skill in the art is commensurate with the scope of protection sought by the claims.

In addition, three articles, all published *after* the priority date of the 10/806,515 application, discuss the effectiveness of bFGF in preventing and treating male erectile dysfunction. A copy of all three articles are attached as Exhibits A, B, and C. These three articles verify what was described in the specification and confirm the rational set forth in the specification that bFGF is useful in the prevention and treatment of ED. A discussion of each of the three articles is provided below.

Xie, D., *et al.*, J. Sexual Medicine, 3:223-232 (2006).

Xie, D., *et al.*, J. Sexual Medicine, 3:223-232 (2006) (hereinafter "Xie"), describes how recombinant basic fibroblast growth factor (rbFGF) may have clinically significant effects in addressing ED in men.

The abstract describes how four groups of rabbits were treated by intracavernosal injection (ICI) with phosphate buffered saline (PBS), rbFGF, or a combination of both. Group 1 was treated twice with only PBS, group 2 was treated once with bFGF and once with PBS, group 3 was treated twice with bFGF, and group 4 was treated only once with bFGF. After sacrifice, strips of corporal tissue were submaximally contracted with norepinephrine, and dose-response curves were generated to evaluate endothelial-dependent (acetylcholine, ACH) and endothelial-independent (sodium nitroprusside, SNP) vasoreactivity. Vasoreactivity was shown to be improved by bFGF treatment as shown by a higher ED50 of ACH and SNP in groups 2-4 as compared to group 1. This lead the investigators to conclude that "ICI of bFGF improved vasoreactivity in hypercholesterolemic rabbit corporeal tissue, *offering a new direction to explore for the treatment of erectile dysfunction.*" (Emphasis added.)

In the Introduction, Xie first describes how "[n]ormal penile erection is predominately a *vascular event* that involves interaction between endothelial and smooth muscle cells in the corpus cavernosum." (Emphasis added.) Xie goes on to describe how "[t]he major etiology of ED is *structural alterations* of the cavernous smooth muscle and endothelium and a resulting decrease in vasomotor reactivity." (Emphasis added.)

Xie describes on page 224, left hand column, how important both VEGF and bFGF are in angiogenesis, "[a]ngiogenesis is the growth and proliferation of blood vessels from existing vascular structures [10]. A number of angiogenic growth factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are known to be present in vascular structures."

Xie also discloses on page 224, left hand column, how the "hypercholesterolemic rabbit model of ED is an established model of nontraumatic vascular injury that results in detrimental structural changes in corporal tissue." Also, on page 228, in the Discussion section, Xie describes how "[i]nitially established in 1991 and further characterized in our laboratory, the

hypercholesterolemic rabbit model of ED is useful for studying corporal endothelial and smooth muscle cells' structure and function."

Xie then describes how in "a prior study, we found that systemic bFGF induces favorable histological changes in the corpus cavernosum of hypercholesterolemic rabbits []. Therefore, the goal of the current effort was to explore the effects of ICI of bFGF on erectile corporal tissue in the same hypercholesterolemic rabbit model." More specifically, as described on page 230, left hand column, "this study was conducted to determine if ICI of bFGF had any therapeutic potential in a rabbit model of ED."

What Xie found, as described in the Results section, starting at page 226, is that "[e]ndothelial-dependent vasoreactivity was improved by rbFGF treatment as shown by higher ED50[-log (M)] of ACH and SNP in Groups 2, 3, and 4 [, with Group 1 being the control group]." Also, they showed that "[a]nimals treated with ICI of bFGF showed greater corporal endothelial cell and smooth muscle cell content vs. control treated rabbits."

Xie summarizes their work on page 230, left hand column, and on page 229, left hand column, in the following manner,

> "[t]he major findings of our current study were that the intracavernous administration of bFGF results in an increase in vasore-activity, endothelial cell content, vascular smooth muscle cell content, bFGF protein, and VEGF protein expression, but no significant increase in corporal tissue fibrosis."

> "At its core ED involves an abnormal interaction between endothelial and smooth muscle cells in the corpus cavernosum [1]. Hypercholesterolemia induces injury to endothelial and vascular smooth muscle cells, resulting in abnormal function and content in preclinical models that bear resemblance to abnormalities found in human corporal tissues [1,2,5,6,9]. *Angiogenic growth factors like VEGF and bFGF are not only [] capable of causing endothelial proliferation, but these cytokines also have the ability to modulate favorably vascular injury.*" (Emphasis added.)

Highlighting the similar mechanisms of action of bFGF and VEGF, on page 230, left hand column, Xie discloses how both factors may act through a similar mechanism to exert beneficial effects on corporal tissue.

> "Generation of nitric oxide (NO) represents the final common element that directly stimulates corporal smooth muscle relaxation [1]. The endothelium-dependent pathway requires the production of NO from corpora endothelium in response to acetycholine from nerves. The endothelial-independent pathway produces smooth muscle relaxation from the direct release of NO from efferent nerve terminals. Angiogenic growth factors may have influence on both processes. VEGF leads to the phosphorylation (and thus activation) of eNOS and has been shown to mediate vascular endothelial growth factor-induced penile erection [30]. The link between bFGF and eNOS is less direct, although bFGF induced eNOS expression in lymphoma cells [31]. In our current study we demonstrated that bFGF treatment promoted eNOS phosphorylation but had no effect on total eNOS levels. Thus, *bFGF and VEGF may act through a similar mechanism (eNOS phosphorylation) to exert beneficial effects on corporal tissue.*" (Emphasis added.)

Furthermore, Xie states on page 231, left hand column, how their "study adds to other studies of VEGF administration and expands the spectrum of the potential use of angiogenic growth factors [including bFGF] to modulate forms of vascular injury, including the treatment of ED."

Xie then concludes on page 231, that

> "[w]e have demonstrated previously that systemic but not intracorporal VEGF can restore corporal vasoactive dysfunction in the NZW rabbit hyper-cholesterolemic model. We now demonstrate that low dosage of bFGF, an angiogenic agent and smooth muscle mitogen, delivered by the intracavernosal route, can also restore endothelial-dependent and independent corporal vasoactive function in this rabbit model. This restoration of vasoactive function may be due to the induction of bFGF protein, VEGF protein, and nNOS activity in hypercholesterolemic rabbit corporal tissue. *These effects suggest that bFGF may have clinically significant effects in addressing ED in men.*" (Emphasis added.)

In summary, Xie shows that: VEGF and bFGF are both important in angiogenesis; both are known to be present in the vascular structures of the penis, like endothelial cells and smooth muscle

cells; vasoreactivity of these cell types was improved by rbFGF treatment; bFGF and VEGF may act through a similar mechanism (eNOS phosphorylation) to exert beneficial effects on corporal tissue; and angiogenic growth factors like bFGF and VEGF are not only capable of causing endothelial proliferation, but these cytokines also have the ability to modulate favorably vascular injury.

It should also be noted that Xie describes the use a hypercholesterolemic rabbit model of ED, which is "an established model of nontraumatic vascular injury that results in detrimental structural changes in corporal tissue." Applicants use a similar hypercholesterolemic model to that described in Xie, although in a rat rather than a rabbit. In the specification, Example 5 describes the effect of a vascular endothelial growth factor (VEGF) and adeno-associated brain derived neurotrophic factor (AAV-BDNF) for the treatment of erectile dysfunction induced by hypercholesterolemia in a rat model.

Therefore, Xie, which was published *after* the priority date of the 10/806,515 application, describes what the inventors disclosed in the specification and claim as their invention, specifically, the importance of bFGF in angiogenesis and maintaining the vascular structure of the penis, how the development and growth of the penile vasculature is governed by bFGF, and thus how bFGF is useful in a method for the prevention and treatment of ED.

Suetomi, T. *et al.*, J. of Urology, 173:1423-1428 (2005).

Suetomi, T. *et al.*, J. of Urology, 173:1423-1428 (2005) (hereinafter "Suetomi"), discloses how bFGF incorporating gelatin microspheres preserve erectile function in a diabetic rat model.

Diabetes mellitus (DM) as it relates to ED and current treatments for DM related ED are described on page 1423.

> "Diabetes mellitus (DM) has been recognized as a major risk factor for erectile dysfunction (ED). The prevalence of ED in men with the disease is almost 3-fold that in the general population."
>
> "A phosphodiesterase 5 inhibitor is recommended as first line treatment for ED. However, efficacy is significantly lower for diabetic ED than for the non-diabetic type due to tissue damage,

> including peripheral nerves, endothelium and smooth muscle in the corpus cavernosum."

In addition, in the Discussion section, it is stated how "[o]ne of the reasons for the low efficacy of ED treatment is considered to be damage to penile vascular structures and cavernous nerves" and how "preservation and restoration of the cavernous tissue, including endothelial cells, cavernous nerve and especially smooth muscle, are needed in patients with diabetes to avoid ED."

The study design is described in the abstract,

> "[a] total of 48 adult male rats were divided into 3 groups, namely control (non-diabetic rats), diabetes mellitus (DM) (diabetic rats that received gelatin microspheres with saline) and bFGF (diabetic rats that received gelatin microspheres with bFGF). After 4 and 8 weeks we examined intracavernous pressure responses with electrical stimulation to the cavernous nerve. For histological examination of the penis we performed Azan-Mallory staining for smooth muscle and collagen, and immunohistochemistry for endothelial nitric oxide synthase (NOS) in endothelium and neuronal NOS in cavernous nerve fiber."

Past experimental success in treating ED with bFGF (published *after* the priority date of the 10/806,515 application), and routes of administration are described on page 1423 and in the Discussion section.

> "Cavernous tissue regeneration is a novel approach for the treatment of ED. There have been some experimental successes in ED treatment using growth factors, such as vascular endothelial growth factor[4], basic fibroblast growth factor (bFGF)[5] and insulin-like growth factor[6]. Since the in vivo half-life of administered growth factor is short, various methods have been used for retaining their activities, such as gene therapy, continuous infusion, repeat injections and sustained release polymers."

> "Many clinical studies achieved favorable results using recombinant bFGF protein for myocardial angiogenesis [15]. In these studies the therapeutic advantages and safety of bFGF have already been confirmed. In an animal experiment the proliferative effect of systemic bFGF for smooth muscle has been shown in hypercholesterolemic rabbit corporeal tissue [5]. Thus, *bFGF is a*

> *promising substance as a growth factor to treat ED clinically.*" (Emphasis added.)

Therefore, not only does Suetomi describe how other groups have treated ED using bFGF, but Suetomi also exemplifies how one of skill in the art would *not* have to undergo undue experimentation to determine the proper route of administration for bFGF.

Suetomi then describes how, in order to address the issue of a short half life, they use gelatin microspheres as a carrier because they have demonstrated sustained biological activity with bFGF. Specifically, in the discussion section,

> "In contrast, gelatin microspheres dissolve via gelatin biodegradation in several weeks. Biodegradation and the duration of bFGF release can be easily controlled through the cross-linking reaction, which leads to the prolongation of activity. Therefore, bFGF incorporating gelatin microspheres showed higher efficacy than the free form of bFGF for myocardial infarction. Our results indicate that sustained release of bFGF from gelatin microspheres was effective for maintaining smooth muscles. Moreover, the biosafety of gelatin has been proved in various foods and in long-term clinical use. Thus, we believe that the gelatin microsphere is an ideal carrier of bFGF."

The results of the study are presented on pages 1427 and 1428.

> "The current study is the first to prove that direct injection of bFGF incorporating gelatin microspheres into the corpous cavernosum can preserve erectile function in a diabetic rat model."

> "This system has the potential for the regeneration of erectile tissue and it can be useful as a new strategy for ED treatment in the future."

> "The current study indicates that bFGF incorporating gelatin microspheres are effective for the preservation of the ICP response and corporeal smooth muscles in a diabetic animal model. These results suggest that this modality can potentially be a novel treatment for ED in the future."

> "In this study we clarified the efficacy of bFGF incorporating gelatin microspheres for diabetic impairment of cavernous tissue."

In summary, Suetomi describes the use of bFGF incorporating gelatin microspheres in diabetic rats as a therapeutic option that is clinically applicable for diabetes induced erectile dysfunction in men.

Dai, Q., *et al.*, J. of Urology. 170: 664-668 (2003).

Dai, Q., *et al.*, J. of Urology. 170: 664-668 (2003) (hereinafter "Dai"), studied the effects of bFGF on erectile corporeal tissue on a hypercholesterolemic rabbit model of erectile dysfunction.

As with Xie above, Dai also describes the importance of an angiogenic growth factors like bFGF in maintaining the proper vascular structure of the penis. (*See* page 664.)

> "Normal penile erection is predominantly a vascular event that involves interaction between endothelial and smooth muscle cells in the corpus cavernosum."
>
> "The major etiology of erectile dysfunction is loss of vascular smooth muscle cell in the corpus cavernosum and a resulting decrease in vasomotor reactivity."
>
> "Angiogenesis is the growth and proliferation of blood vessels from existing vascular structures. A number of angiogenic growth factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are known to be present in vascular structures."
>
> "Angiogenic growth factors can act as survival factors for micro-vascular endothelium and help endothelial cells avoid cell death (apoptosis) when subject to injury. This feature should be beneficial to corporeal endothelial cells during high cholesterol feeding."

The results of the study are described in the Discussion section.

> "The major findings of the current study were that the systemic administration of bFGF results in an increase in vascular smooth muscle with no change in endothelial cell content, an increase in VEGF protein expression and no significant increase in corporeal tissue fibrosis. Trabecular smooth muscle content is the key structure in normal erectile function and the degree of loss of corporeal smooth muscle content correlates with the extent of impairment in corporeal veno-occlusive function. Therefore, our findings suggest that *bFGF*

> *may be valuable in the therapeutic modulation of erectile dysfunction*." (Emphasis added.)

As summarized in the last paragraph on page 667, Dai discloses the use of bFGF to "modulate forms of vascular injury, including the treatment of erectile dysfunction."

The specification describes routes of administration for bFGF.

The specification provides ample description as to how one of skill in the art could determine the proper route of administration for bFGF.

As described at paragraph 31,

> "[t]he formulation, dosage and route of administration of the above-described compositions, combinations, preferably in the form of pharmaceutical compositions, can be determined according to the methods known in the art (see *e.g.*, *Remington: The Science and Practice of Pharmacy*, Alfonso R. Gennaro (Editor) Mack Publishing Company, April 1997; *Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems*, Banga, 1999; and *Pharmaceutical Formulation Development of Peptides and Proteins*, Hovgaard and Frkjr (Ed.), Taylor & Francis, Inc., 2000; *Medical Applications of Liposomes*, Lasic and Papahadjopoulos (Ed.), Elsevier Science, 1998; *Textbook of Gene Therapy*, Jain, Hogrefe & Huber Publishers, 1998; *Adenoviruses: Basic Biology to Gene Therapy*, Vol. 15, Seth, Landes Bioscience, 1999; *Biopharmaceutical Drug Design and Development*, Wu-Pong and Rojanasakul (Ed.), Humana Press, 1999; *Therapeutic Angiogenesis: From Basic Science to the Clinic*, Vol. 28, Dole *et al.* (Ed.), Springer-Verlag New York, 1999). The compositions, combinations or pharmaceutical compositions can be formulated for oral, rectal, topical, inhalational, buccal (*e.g.*, sublingual), parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), transdermal administration or any other suitable route of administration. The most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular composition, combination or pharmaceutical composition which is being used."

In addition, examples of routes of administration are described at paragraph 80,

> "[a]ccording to the present invention, the VEGF, BDNF, or bFGF peptides, proteins, polynucleotides, nucleic acids, or agent that

> enhances production and/or erection or sexual arousal stimulating function of said factor may be formulated for intracavernous injection, subcutaneous injection, intravenous injection, intramuscular injection, intradermal injection, or topical administration. The method may employ formulations for injectable administration in unit dosage form, in ampules or in multidose containers, with an added preservative. The formulations may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, sterile pyrogen-free water or other solvents, before use. Topical administration in the present invention may employ the use of a foam, gel, cream, ointment, transdermal patch, or paste."

Paragraph 86, goes on to describe how "[a]ny suitable route of administration may be used. Dosage forms include tablets, troches, cachet, dispersions, suspensions, solutions, capsules, patches, and the like. See, Remington's Pharmaceutical Sciences."

Lastly paragraph 87 discloses how,

> "[i]n practical use, VEGF, BDNF, or bFGF peptides, proteins, polynucleotides, nucleic acids, or agent that enhances production and/or erection or sexual arousal stimulating function of said factor may be combined as the active in intimate admixture with a pharmaceutical carrier or incipient according to conventional pharmaceutical compounding techniques. The carrier may take a wide form of preparation desired for administration, topical or parenteral. In preparing compositions for parenteral dosage form, such as intravenous injection or infusion, similar pharmaceutical media may be employed, water, glycols, oils, buffers, sugar, preservatives, liposomes, and the like known to those of skill in the art. Examples of such parenteral compositions include, but are not limited to dextrose 5% w/v, normal saline or other solutions. The total dose of VEGF, BDNF, or bFGF to be administered may be administered in a vial of intravenous fluid, ranging from about 1 ml to 2000 ml. The volume of dilution fluid will vary according to the total dose administered."

Therefore, one of skill in the art, armed with the guidance provided by the specification in regards to how to determine the proper route of administration for bFGF, would not have to undergo undue experimentation to practice the claimed methods.

Accordingly, in light the amendments to claim 1 and the arguments set forth above and in the § 1.132 Declaration filed herewith, Applicants respectfully submit that claims 1, 4, 5, 9, 11-15, 21, 23-28 and new claims 29-39 are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Other Family Members (Applications)

Applicants wish to call the attention of the Examiner to the prosecution of the parent application and to the prosecution of other applications in the same family.

The parent application, based on Serial No. 09/909,544, filed 19 July 2001, has issued as U.S. Patent No. 6,852,323. Another application that also claims priority to the parent, namely U.S. 10/155,785, filed 23 May 2002, has been issued a Notice of Allowance. Lastly, in U.S. 11/040,847, filed 21 January 2005, that claims priority to U.S. 10/155,785, the Examiner has verbally indicated to Applicants that the pending claims will be allowed.

In all three of these cases, the aspects of the claims related to treating female sexual arousal disorder were subject to a rejection under 35 U.S.C. § 112, first paragraph, and this aspect of the claims was canceled to expedite prosecution.

CONCLUSION

In view of the arguments provided above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **220022001610**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-7961.

Dated: May 15, 2007

Respectfully submitted,

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